IN THE SPECIFICATION

Please replace paragraph [0003] with new paragraph [0003] below:

[0003] The World Health Organization (WHO) has classified NPC into three categories according to the degree of differentiation (Marks et al., 1998). Type I refers to squamous cell carcinomas which are highly differentiated with characteristic epithelial growth patterns and intra- and extra-cellular keratin filaments. Non-keratinizing WHO type II carcinomas retain epithelial cell shape and growth patterns. WHO type III undifferentiated carcinomas, on the other hand, produce no keratin and have no distinctive growth pattern. WHO-I keratinizing squamous cell carcinoma comprised 75% of the U.S. nasopharyngeal carcinoma cases and were found most in U.S.-born, non-Hispanic whites. WHO-II non-keratinizing and WHO-III undifferentiated carcinomas of the nasopharynx comprised the remaining 25% of NPC and were more common in Asians. Clinically, Asians were reported to have the highest proportion of radioresponsive WHO-II nonkeratinizing and WHO-III undifferentiated carcinomas of the nasopharynx and better survival in comparison to African-Americans and Hispanic and non-Hispanic whites, who had the greatest number of the less radioresponsive kertinizing squamous cell carcinomas of the nasopharynx. The 5-year relative survival was reported to be 65% for the nonkeratinizing and undifferentiated carcinomas of the nasopharynx and 37% for the keratinizing variety (Marks et al., 1998).

Please replace paragraph [0043] with new paragraph [0043] below:

[0043] As mentioned above, type II and type III undifferentiated NPC are more responsive to radiotherapy and consequently there is a better survival rate in patients suffering from these types of NPC. The present inventors have determined a number of genes that are up-regulated in undifferentiated NPC as opposed to differentiated, type I NPC (see Table 1). These genes include H19 and CDKN1C.

Please replace paragraph [0086] with new paragraph [0086] below:

[0086] The protocol accompanying the 3DNA Expression Array Detection Kit (Genisphere Inc.,

Montvale, N.J.) for the synthesis of hybridization probes was used, with modifications. cDNA was synthesized by reverse transcription using 10 μg of total RNA extracted from human NPC cells or from 10 μg of reference RNA (pooled from 10 cell lines) with oligo(dT) primers incorporating either the capture sequence for the 3DNA Cy5 'labeling' reagent (5'- CCTGTTG CTCTATTTCCCGTGCCGCTCCGGT-$(dT)_n$-3') (SEQ ID NO:1) or the 3DNA Cy3 'labeling' reagent (5'GGCCGACTCACTGCGCGTCTTCTGTCCCGCC-$(dT)_n$-3') (SEQ ID NO:2), respectively. The 10 cell lines from which the pooled reference RNA was generated were A498, A549, DAKIKI, CNE-2, Fadu, HeLa, HepG2, MCF-7, HT-3, and K562. cDNAs generated from each of the test RNA samples (CNE-2 or HK1) as well as the reference RNA were competitively hybridized to the microarray using a hybridization volume of 20 μl under a glass coverslip and in a dark humidified chamber (TeleChem International Inc, Sunnyvale, Calif.) overnight at 42° C.

Please replace paragraph [0088] with new paragraph [0088] below:

[0088] Hybridized arrays were scanned with a GMS 418 laser scanner (Genetic Microsystems Inc, Woburn, Mass.). Images for Cy5 and Cy3 were acquired separately using different channels, superimposed and quantified with Imagene software version 3.0 (BioDiscovery Inc, Los Angeles, Calif.). Spots on the array were defined by aligning a grid of circles over each spot on the entire array image. The net signal for each spot was obtained by subtracting the background signal from the average intensity within the spot. The signal intensities obtained from both Cy5 and Cy3 channels were normalized by applying a scaling factor such that the mean Cy5:Cy3 ratio of spots across the entire array is 1.0. $Log_2$-transformation and centering of the median for the Cy5:Cy3 ratio were then computed. A hierarchical clustering algorithm was applied using complete linkage clustering (Gene Cluster program, http://rana.lbl.gov/; Eisen et al., 1998). The TreeView program (Eisen et al., 1998) was used to visualize the clustered data by displaying the intensity of gene expression using a spectrum of graded colors from bright red, through black, to bright green. Unfortunately, this cannot be shown in the black and white figures accompanying this specification. However, the intensities have been indicated by differently marked boxes. See, for example, FIG. 1.

Please replace paragraph [0091] with new paragraph [0091] below:

[0091] Seven cell lines (CNE-2, HK1, HeLa, Hep-G2, HT-3, NIH:OVCAR-3 and SW480) were cultured separately for 7 days in RPMI (containing 10%; fetal bovine serum) in the presence or absence of 12.5 μM 5'-aza-2'-deoxycytidine (Sigma Diagnostics, St. Louis, Mo.). Total RNA from these cell lines was extracted using TRIzol Reagent (Gibco BRL, Life Technologies, Grand Island, N.Y.), according to manufacturer's instruction. Twenty μg of total RNA was used for Northern blot analysis.

Please replace paragraph [0092] with new paragraph [0092] below:

Bisulphite Sequencing of the H19 Promoter Region

[0092] Genomic DNA (2 μg) was digested with RsaI at 37° C. for 16 h and denatured by adding freshly prepared NaOH to a final concentration of 0.3M at 42° C. for 30 min. The bisulphite reaction was carried out on the denatured DNA by adding urea/bisulphite solution and hydroquinone to final concentrations of 5.36M, 3.44M and 0.5 mM respectively. The reaction involves 20 cycles of 55°C. (15 minutes) followed by denaturation at 95° C. (30 seconds). The bisulphite-treated DNA (5 .mu.l) was amplified by PCR in a 20 μl reaction with 0.5 units of AmpliTaq DNA polymerase (Perkin-Elmer Corp., Norwalk, Conn.) and using primers (10 .mu.M) that will amplify a 306-bp region in the H19 promoter: 5'-AGATAGTGG TTTGGGAGGGAGAGGTTTTGGAT-3' (SEQ ID NO:3)and 5'-ATCCCACCCCCTCCCTCACCCTACT CCTCA-3' (SEQ ID NO:4). The reaction was subjected to 94° C. (3 minutes), then 35 cycles (of 94° C. for 30 seconds, 58° C. for 1 minute, 72° C. for 30 seconds), and ending with 72° C. (6 minutes). The bisulphite-treated DNA was then cloned and sequenced as described (Tremblay et al., 1997). DNA sequencing was carried out using a CEQ 2000 capillary sequencer (Beckman Coulter Inc., Fullerton, Calif.).

Please replace paragraph [0095] with new paragraph [0095] below:

[0095] Gene expression profiles were established using RNA extracted from the undifferentiated human NPC cell line CNE-2 and the well-differentiated NPC cell line HK1 and hybridized to spotted microarrays. CNE-2 and HK1 cells exhibited distinct gene expression profiles (FIG. 1, Table 1). Six genes out of the approximately 1000 genes studied were found to be consistently up-regulated in the HK1 cells in comparison to the CNE-2 cells (Table 1). These include the genes that encode

metallothionein-I, human melanoma-associated antigen B3, and monocyte chemotactic protein-3 (MCP-3) (FIG. 1A, Table 1). In comparison, there are fifteen genes that were found consistently to be more highly expressed in the RNA of the undifferentiated CNE-2 cells than that of the well-differentiated HK1 cells (Table 1). Some of these genes include the H19 imprinted gene, the cyclin-dependent kinase inhibitor 1C (CDKN1C or p57KIP2) gene, genes that encode protein-tyrosine kinase Flt4, Tat-interacting protein, and cyclin D3 (FIG. 1B and C, Table 1).

Please replace paragraph [0104] with new paragraph [0104] below:

[0104] Human NPC are classified into Types I, II, and III according to their degrees of differentiation and keratinization (Marks et al., 1998). Type I is the squamous cell NPC carcinomas that are highly differentiated and relatively less radioresponsive. Type III undifferentiated NPC carcinomas, on the other hand, are more radioresponsive (Neel 1985; Marks et al., 1998). The molecular mechanism for tumor promotion and progression in human NPC is, at best, partially understood and there is no study on the relationship of the differentiation status of NPC cells and carcinogenesis. Genetic alterations have been implicated as one of many mechanisms likely to contribute towards the development of NPC. Most of these genetic alterations will be reflected by a subsequent change in the respective gene products. In Singapore, it has been suggested that more than 90% of clinically detected NPC cases are poorly differentiated. In this study, the inventors have therefore employed cDNA microarrays to identify genes whose expression differs in well-differentiated and undifferentiated NPC carcinoma cells. These genes will undoubtedly be important for elucidating human NPC carcinogenesis. From their cDNA microarray analyses, fifteen genes were demonstrated to be differentially upregulated in the undifferentiated CNE-2 NPC cells, while six genes were specifically upregulated in the well-differentiated HK1 cells (FIG. 1 and Table 1).

Please replace paragraph [0116] with new paragraph [0116] below:

[0116] Casola S, Pedone, P V, Cavazzana A O, Basso G, Luksch R, d'Amore E S, Carli M, Bruni C B, Riccio A (1997) Expression and parental imprinting of the H19 gene in human rhabdomyosarcoma. Oncogene 14: 1503-1510

Please replace paragraph [0128] with new paragraph [0128] below:

[0128] Hatada I, Inazawa J, Abe T, Nakayama M, Kaneko Y, Jinno Y, Niikawa N, Ohashi H, Fukushima Y, Iida K, Yutani C, Takahashi S, Chiba Y, Ohishi S and Mukai, T (1996) Genomic imprinting of human p57KIP2 and its reduced expression in Wilms' tumors. Hum Mol. Genet 5: 783-788